Election

The Examiner issued a Restriction Requirement under 35 U.S.C. 121 in the above-identified application, grouping the claims as follows: Group I, claims 1-13, 21-24, and 28-71 drawn to a method of detecting metastatic cells, classified in class 435, subclass 7.1, Group II, claims 14-16, and 89, drawn to a method of producing an antibody, classified in class 530, subclass 387.1, Group III, claims 17-20, 25-27, and 84-88, drawn to an antibody and kit, classified in class 530, subclass 387.9; Group IV, claims 72-81, drawn to a method detecting cancer cells, classified in class 435, subclass 7.1; and Group V, claims 82-83, drawn to the D7 hybridoma cell line, classified in class 435, subclass 326. A provisional election to prosecute claims 1-13, 21-24 and 28-71, Group I, was made in response to a telephone conversation with the Examiner on **18 May 2001**. The provisional election to prosecute Group I is herein affirmed with traverse.

Applicants respectfully request modification of the restriction requirement. It is respectfully submitted that Group I, claims 1-13, 21-24, and 28-71 drawn to a method of detecting metastatic cells, classified in class 435, subclass 7.1, and Group IV, claims 72-81, drawn to a method detecting cancer cells, classified in class 435, subclass 7.1, can be readily evaluated in one search without placing undue burden on the Examiner, as both groups are classified in the same class and subclass. That is, all the claims are so interrelated that a search of one group of claims will reveal art to the others. Were restriction to be effected between the claims of Groups I and IV, a separate examination of the claims in these two groups would require substantial duplication of work on the part of the U.S. Patent and Trademark Office. Applicants, therefore, respectfully request modification of the restriction requirement to include restriction to the invention of Groups I and IV (claims 1-13, 21-24, and 28-81).

The 35 U.S.C. §103(a) Rejection

The Examiner rejected claims 1-8, 10-13, 21-24, and 28-71 under 35 U.S.C. §103(a) as unpatentable over Pasquale, et al. (U.S. Patent No. 5,457,048) in view of Zantek, et al., "Cell Adhesion and Signaling," Mol. Bio. Cell, 9 (Supp); 134a, abstract 773, 38th Annual Meeting of the American Society for Cell Biology (1998), and Kinch, et al., "Identification of Tyrosine Phosphorylated Adhesion Proteins in Human Cancer Cells," Hybridoma, 17, 227-235 (1998). Applicants respectfully traverse this rejection.

Applicant respectfully submits that the document by Zantek, et al., entitled "Cell Adhesion and Signaling," Mol. Bio. Cell, 9 (Supp); 134a, abstract 773, cited herein by the Examiner, is not a prior art with respect to the elected claims. The supplement to volume 9 of the journal *Molecular Biology of the Cell*, which contained the abstracts for the 38th Annual Meeting, was mailed in November, 1998. This information was obtained from the American Society for Cell Biology, as indicated in the Declaration of Kathleen L. Franklin, included herewith. The present application claims priority to a provisional application filed August 17, 1999, which is within one year of the publication date of the Zantek et al. abstract.

Two of the authors of the Zantek et al. abstract, Nicole Zantek and Michael Kinch, are the joint inventors of the claims elected and under examination in the present application. The other two co-authors of the Zantek et al. abstract, Mary Fedor-Chaiken and Robert Brackenbury, are not inventors of the subject matter of the elected claims or of the information that is commonly disclosed in the present application and in the published abstract on which the Examiner is basing the rejection. Mary Fedor-Chaiken and Robert Brackenbury are co-authors of the Zantek et al. abstract solely because they provided to Drs. Zantek and Kinch cells in which they had overexpressed E-cadherin. Neither Mary Fedor-Chaiken nor Robert Brackenbury participated in the studies of EphA2 overexpression in cancer cells, the subject matter commonly disclosed in the Zantek et al. abstract, in the above-identified Patent Application Serial No. 09/640,952, and in the Provisional Application, Serial No. 60/149,259, filed August 17, 1999. The Examiner's attention is directed to the In re Katz Declaration of Michael S. Kinch, Ph.D. In

view of the In re Katz Declaration of Michael S. Kinch and the above comments, it is respectfully requested that the Zantek et al. abstract cited by the Examiner be removed as a reference under 35 U.S.C. §102/103.

Pasquale et al. teach the identification and characterization of seven novel members of the Eph subclass of receptor tyrosine kinases and their use in diagnosing aberrations in normal cellular processes (Pasquale et al., column 4, lines 23-25 and 63-65). Pasquale et al., as noted by the Examiner on page 4 of the Office Action dated July 5, 2001, do not teach the use of EphA2 receptor tyrosine kinase. Further, although Pasquale et al. teach that the distinct tissue distribution patterns exhibited by the disclosed tyrosine kinases can be used to diagnose aberrations in normal cellular processes, such as those leading to uncontrolled malignant cell growth (Pasquale et al., column 4, lines 54-65), Pasquale et al. neither teach nor suggest that the EphA2 receptor tyrosine kinase could also be used to diagnose aberrations in normal cellular processes. In fact, Pasquale et al. teach away from the suggestion that any of the Eph-related kinases, including EphA2, can be successfully substituted for the disclosed Eph-related tyrosine kinases by teaching that:

(1) "[t]he number of existing Eph-related kinases is not known and cannot be predicted", and "[t]here is no indication whether other Eph-related kinases exist and, if [they do exist], what their relationship is to the known Eph-related kinases" (Pasquale et al., column 2, lines 45-46 and 60-62);

(2) despite some "common structural features [of the Eph subclass of receptor tyrosine kinases], the overall amino acid sequences outside the catalytic domain are quite different, indicating that different members of the Eph subclass interact with distinct ligands and substrates and, thus, exert distinct functions" (Pasquale et al., column 2, lines 53-57); and

(3) "despite similarities among Eph-related receptor tyrosine kinases, each is different and, as such, functions in related but distinct cellular processes" (Pasquale et al., column 2, lines 62-65).

Therefore, Pasquale et al. provide no motivation to use the EphA2 receptor kinase to diagnose aberrations in normal cellular processes, and even if the modification was made, Pasquale et al teach away from the invention by implying that success could not reasonably be expected.

This defect is not remedied by the teachings of Kinch et al. Kinch et al. teach techniques to generate monoclonal antibodies that bind to a class of proteins, namely tyrosine phosphorylated proteins (Kinch et al, page 233, column 1, last 3 lines). Kinch et al. teach that disclosed antibodies, including D7 and B2D6, bind to tyrosine phosphorylated proteins; however, Kinch et al. neither teach nor suggest that any specific antibody, including D7 and B2D6, bind to any specific tyrosine kinase, including the tyrosine kinase EphA2. Moreover, Kinch et al. is not an enabling disclosure of antibodies D7 and B2D6 because the hybridomas that make those antibodies were not publicly available (they were deposited with the ATCC under the Budapest Treaty on December 8, 2000). Thus, one of skill in the art, even if motivated to do so, would not have been able to further characterize D7 and B2D6, discover that they bind EphA2, and then proceed to further characterize EphA2 and its role in cancer etiology to yield the claimed methods.

Finally, Pasquale et al. and Kinch et al., even if combined, do not teach or suggest all the limitations of the claimed invention. Applicants' claimed invention recites a method for detecting metastatic or potentially metastatic cells in a population that includes, *inter alia*, the use of a reagent capable of binding to EphA2, to an epitope of EphA2, or to a compound associated with EphA2 expression. Neither reference teaches an EphA2 kinase. Pasquale et al. teach the use of tyrosine kinases other than EphA2 for diagnosing aberrations in normal cellular processes. Kinch et al. teach antibodies that bind with certain tyrosine kinases in general, but they do not teach which antibodies bind which tyrosine kinases. Specifically, Kinch et al. do not teach that which is missing from Pasquale et al., which is that D7 and B2D6 bind EphA2 tyrosine kinase and that EphA2 is associated with cancer etiology.

It is respectfully submitted that the Examiner has not sustained a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection of claims 1-8, 10-13, 21-24, and 28-71 under 35 U.S.C. §103(a) is, therefore, respectfully requested.

Summary

It is respectfully submitted that claims 1-13, 21-24, and 28-81 (Groups I and IV), presently pending in the instant application, are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EL 888271719 US Date of Deposit: October 5, 2001
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

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